D E C L A R A T I O N

In the matter of U.S. Patent Application Ser. No. 10/530,046 in the name of Yukiko YOKOI et al.

I, Natsumi ITO, of Kyowa Patent and Law Office, 2-3, Marunouchi 3-Chome, Chiyoda-Ku, Tokyo-To, Japan, declare and say:

that I am thoroughly conversant with both the Japanese and English languages; and,

that the attached document represents a true English translation of Japanese Patent Application No. 2002-290367 filed on October 2, 2002.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Natsumi ITO

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Title of the Invention: ANTIBIOTIC PHARMACEUTICAL COMPOSITION WITH IMPROVED ORAL ABSORBABILITY

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[Title of Invention] ANTIBIOTIC PHARMACEUTICAL COMPOSITION WITH IMPROVED ORAL ABSORBABILITY

[Claims]

[Claim 1]

A solid composition comprising a physical mixture of amorphous cefditoren pivoxil and a sucrose ester of fatty acid.

[Claim 2]

The solid composition according to claim 1, which contains 0.1 to 100 mg of the sucrose ester of fatty acid on the basis of an amount equivalent to 100 mg efficacy of cefditoren pivoxil.

[Claim 3]

The solid composition according to claim 1 or 2, which further comprises a pharmaceutically acceptable polymer.

[Claim 4]

The solid composition according to claim 3, wherein the polymer is one or more water-soluble high polymers selected from hydroxypropylmethyl cellulose, methylcellulose, hydroxyethyl cellulose, polyvinylpyrrolidone, and hydroxypropyl cellulose.

[Claim 5]

The solid composition according to claim 3 or 4, which contains 1 to 100 mg of the polymer on the basis of an amount equivalent to 100 mg efficacy of cefditoren pivoxil.

[Detailed Description of the Invention]

[0001]

[Field of the Invention]

The present invention relates to antibiotic pharmaceutical compositions with improved oral absorbability, more specifically to antibiotic pharmaceutical compositions comprising amorphous cefditoren pivoxil.

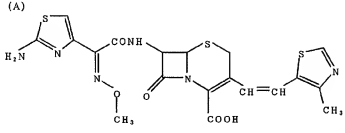
[0002]

[Background Art]

An antibiotic ompound cefditoren is a cephem compound represented by formula (A):

[Formula 1]

(A)



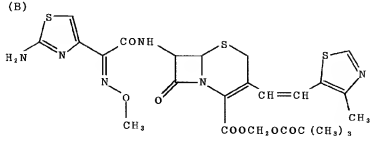
Its chemical name is (+)-(6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(Z)-2-(4-methylthiazol-5-yl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. This compound is described in Japanese Patent Pub. No. 3 (1991)-64503 (Patent Document 1) under the chemical name of 7-[2-methoxyimino-2-(2-aminothiazol-4-yl)acetamido]-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cephem-4-carboxylic acid (syn-isomer, cis-isomer).

[0003]

A pivaloyloxymethyl ester of cefditoren, in which a carboxylic acid group on position 2 of the cephem compound is esterified with a pivaloyloxymethyl group for the purpose of improving its absorbability through the digestive tracts upon oral administration (hereinafter sometimes referred to simply as "oral absorbability"), is called cefditoren pivoxil. This prodrug compound is represented by formula (B):

[Formula 2]

(B)



and its chemical name is (-)-(6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(Z)-2-(4-methylthiazol-5-yl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 2,2-dimethylpropionyloxymethyl ester. This ester compound is generally considered to exhibit high oral absorbability as compared to the original acid-form drug. However, the esterification of cefditoren has not necessarily resulted in enhancement or improvement of the oral absorbability to the satisfactory level.

[0004]

In order to improve the oral absorbability of cefditoren pivoxil, a pharmaceutical preparation in which cyclodextrin or hydroxypropyl cellulose that is a water-soluble cellulosic polymer derivative is added to cefditoren pivoxil has been proposed (Japanese Patent Pub. No. 6 (1994)-78234 (Patent Document 2) and Japanese Patent Laid-Open Pub. No. 7 (1995)-17866 (Patent Document 3)). However, the addition of cyclodextrin to cefditoren pivoxil extremely intensified the bitterness derived from cefditoren pivoxil and pharmaceutical tablets or granules obtained with the addition of hydroxypropyl cellulose caused a problem of becoming bulky, which made oral administration difficult.

[0005]

In order to solve these problems, a pharmaceutical preparation in which a water-soluble caseinate is added to cefditoren pivoxil has recently been proposed (Japanese Patent No. 2831135 (Patent Document 4)). However, this preparation could not be administered to a patient suffering from a milk allergy since casein is a protein derived from milk.

[0006]

Thus, a pharmaceutical preparation wherein cefditoren pivoxil can be safely administered to a patient and oral absorbability sufficient enough to exert its expected pharmaceutical effect is secured has been in demand.

[0007]

On the other hand, as a means to improve oral absorbability of a poorly soluble drug, a solid composition which is obtained by amorphousizing the poorly soluble drug in the presence of a polymer base and a nonionic surfactant is disclosed in WO 96/19239

(Patent Document 5). It is disclosed that the above-mentioned composition maintains its amorphousness state when dispersed in a liquid and that the maximum concentration in the blood (Cmax) and the area under the curve of blood concentration (AUC) increase when orally administered to dogs, that is, the oral absorbability can be improved. However, shortening of the time required to reach the maximum blood concentration (Tmax), which is an index of immediate effect, has not been achieved. Further, since the disclosed solid composition contains a nonionic surfactant at a high formulation ratio and this makes the pharmaceutical preparation bulky, the disclosed solid composition is not applicable to a high-content pharmaceutical preparation containing, for example, not less than 100 mg of a nonionic surfactant as a drug. Further, the disclosed solid composition is notably characterized in that the drug, the polymer base, and the nonionic surfactant are mixed in a molecular state, namely in a state of solid dispersion composition. Furthermore, such a pharmaceutical preparation is produced using a spray drying method in which a solvent such as dichloromethane is occasionally used, which requires a concern for environment and a security for safety.

[0008]

Further, Japanese Patent No. 3290970 (Patent Document 6) discloses, as a means to improve oral absorbability of a poorly soluble drug, a solid pharmaceutical preparation containing poorly soluble NSAIDs, a water-soluble polymer base and a nonionic surfactant, which is characterized in that the poorly soluble NSAIDs are in a crystalline state.

[0009]

Further, WO 99/34832 (Patent Document 7) discloses a composition comprising a crystallographically stable, amorphous cephalosporin and a process for the preparation thereof, indicating that the oral absorbability can be improved by amorphousizing the cephalosporin. Further, Japanese Patent Laid-Open Pub. No. 2001-131071 (Patent Document 8) discloses a process for the preparation of amorphous cefditoren pivoxil, in which the oral absorbability can be improved by amorphousizing cefditoren pivoxil.

[0010]

[Patent Document 1]

Japanese Patent Pub. No. 3 (1991)-64503

[Patent Document 2]

Japanese Patent Pub. No. 6 (1994)-78234

[Patent Document 3]

Japanese Patent Laid-Open Pub. No. 7 (1995)-17866

[Patent Document 4]

Japanese Patent No. 2831135

[Patent Document 5]

WO 96/19239

[Patent Document 6]

Japanese Patent No. 3290970

[Patent Document 7]

WO 99/34832

[Patent Document 8]

Japanese Patent Laid-Open Pub. No. 2001-131071

[0011]

[Problems to be Solved by the Invention]

However, the present inventors confirmed that a suspension in which crystals of cefditoren pivoxil were sufficiently suspended exhibited extremely low oral absorbability in dogs as compared to an amorphous suspension. As a result, it was found that the process disclosed in Japanese Patent No. 3290970 was not practically applicable to cefditoren pivoxil. On the other hand, since amorphous cefditoren pivoxil is apt to change into a crystalline state in a solution, an antibiotic pharmaceutical composition comprising amorphous cefditoren pivoxil still needs to be improved.

[0012]

Thus, an objective of the present invention is to provide a cefditoren pivoxil pharmaceutical preparation which can safely be administered to a patient and not only improves wettability of cefditoren pivoxil, but also further improves absorbability through the intestinal tracts by maintaining amorphous particles having high oral absorbability in a liquid for a long period of time.

[0013]

[Means for Solving the Problems]

The present inventors have now found that crystallization of amorphous cefditoren pivoxil in a solvent was inhibited by simply mixing a sucrose ester of fatty acid with amorphous cefditoren pivoxil. This finding was surprising because various surfactants are apt to promote crystallization of amorphous substances. The present inventors also confirmed that the pharmaceutical preparation comprising a simple mixture of an amorphous cefditoren pivoxil and a sucrose ester of fatty acid actually inhibited high oral absorbility. The present invention was made on the basis of these findings.

[0014]

Namely, the present invention is a solid composition comprising a physical mixture of amorphous cefditoren pivoxil and a sucrose ester of fatty acid.

[0015]

The solid composition according to the present invention is advantageous in that the amorphous state of amorphous cefditoren pivoxil can be maintained for a long period of time and that the oral absorbability and the immediate effect of cefditoren pivoxil are excellent. Further, the solid composition according to the present invention is expected to have high dispersibility and elutability in an aqueous solution because of its excellent wettability. The solid composition according to the present invention is advantageous in that its production process is simple and does not cause any safety or environmental problem because it can be produced by simply mixing amorphous cefditoren pivoxil with a sucrose ester of fatty acid or the like without use of any solvent in the formulation process. The solid composition according to the present invention is also advantageous in that it may contain the sucrose ester of fatty acid at a low formulation relative to entire components and that the obtained pharmaceutical preparation is not bulky.

[0016]

[Best Mode for Carrying Out the Invention]

Amorphous cefditoren pivoxil which is commercially available or produced in accordance with a known method can be used as an effective component in the solid composition according to the present invention. Amorphous cefditoren pivoxil can be

produced in accordance with, for example, Japanese Patent Pub. No. 3 (1991)-64503, WO 99/34832, and Japanese Patent Laid-Open Pub. No. 2001-131071.

[0017]

A sucrose ester of fatty acid added to the solid composition according to the present invention can be used by selecting from commercially available products.

[0018]

The sucrose ester of fatty acid can be, but not particularly limited to, any ester which is pharmaceutically acceptable and extends the amorphousness-maintaining period for amorphous cefditoren pivoxil, and a hydrophilic ester having a high HLB value is preferred and, for example, one with an HLB value of more than 10, preferably 15 to 20, can be used. The HLB value can be calculated in accordance with "Standard Methods for Analysis of Fats and Oil" (1971) edited by Japan Oil Chemist's Society. The sucrose ester of fatty acid can be used singly or as a mixture of two or more kinds thereof, if necessary.

[0019]

The amount of the sucrose ester of fatty acid to be added can be 0.1 to 100 mg, preferably 0.1 to 5 mg, on the basis of an amount equivalent to 100 mg efficacy of cefditoren pivoxil.

[0020]

Preferably, the solid composition according to the present invention can further contain a pharmaceutically acceptable polymer. The amorphousness-maintaining period for amorphous cefditoren pivoxil can be markedly extended by adding a pharmaceutically acceptable polymer together with a sucrose ester of fatty acid.

[0021]

The pharmaceutically acceptable polymer to be added can be used by selecting from commercially available products.

[0022]

The polymer can be, but not particularly limited to, any polymer which does not inhibit the extension of the amorphousness-maintaining period for amorphous cefditoren pivoxil or further extends the amorphousness-maintaining period, and a pharmaceutically acceptable water-soluble polymer can be preferably used.

[0023]

Examples of the polymers usable include hydroxypropylmethyl cellulose (HPMC), methylcellulose (MC), hydroxyethyl cellulose (HEC), polyvinylpyrrolidone (PVP), and hydroxypropyl cellulose (HPC), and the like, preferably, HPMC, MC, and HEC. The polymer can be used singly or as a mixture of two or more kinds thereof, if necessary.

[0024]

The amount of the polymer to be added can be 1 to 100 mg, preferably 1 to 50 mg, on the basis of an amount equivalent to 100 mg efficacy of cefditoren pivoxil.

[0025]

The solid composition according to the present invention comprises a mixture obtained by physically mixing individual components. The "physical mixture" as mentioned in this specification means a mixture obtained by simply mixing individual components, and is distinguished from a mixture obtained by temporarily dissolving individual components in a solvent followed by the removal of the solvent. At the time of mixing, the individual components in a form of power may be mixed or the individual components in a solid state can be crushed in the process of mixing.

[0026]

The solid composition according to the present invention can be formulated into various dosage forms as a pharmaceutical preparation suitable for oral administration. Examples of the pharmaceutical preparations suitable for oral administration include powders, fine granules, granules, tablets, and capsules. The pharmaceutical preparation suitable for oral administration can be produced by an ordinary method using pharmaceutically acceptable additives to be used ordinarily, such as excipients, fillers, binding agents, wetting agents, disintegrants, surfactants, lubricants, dispersants, buffering agents, preservatives, solution adjuvants, antiseptics, flavoring agents, analgesic agents, and stabilizers.

[0027]

The amount of cefditoren pivoxil in the solid composition varies depending on its dosage form, and can be 5 to 90% by weight, preferably 10 to 80% by weight of the entire composition. The amount of administration for the treatment and prevention of bacterial infection or the like can be appropriately determined by considering the usage, the

age and gender of the patient, the severity of the symptoms, and the like, and an appropriate dose for an adult may be about 300 to 800 mg per day, which can be administered daily as a single or divided dose.

[0028]

[Examples]

The present invention will be further illustrated in detail by the following examples that are not intended to restrict the scope of the present invention.

[0029]

Reference Examples 1 to 5 and Examples 1 to 5

A homogenous powder mixture was obtained by mixing amorphous cefditoren pivoxil and surfactants at the formulation ratios shown in Table 1. The amorphous cefditoren pivoxil was prepared in accordance with WO 99/34832.

[0030]

[Table 1]

	Surfactant	Formulation ratio (drug:surfactant)
Reference Example 1	-	100 mg efficacy : -
Example 1	Sucrose ester of fatty acid (DK Ester SS, HLB value = 20, Daiichi Kogyo Seiyaku Co.,Ltd.)	100 mg efficacy : 5 mg
Example 2	Sucrose ester of fatty acid (DK Ester F-140, HLB value = 13, Daiichi Kogyo Seiyaku Co.,Ltd.)	100 mg efficacy : 5 mg
Example 3	Sucrose ester of fatty acid (DK Ester F-110, HLB value = 11, Daiichi Kogyo Seiyaku Co.,Ltd.)	100 mg efficacy : 5 mg
Example 4	Sucrose ester of fatty acid (Surfhope J-1811, HLB value = 11, Mitsubishi Kagaku Foods Corporation)	100 mg efficacy : 5 mg
Example 5	Sucrose ester of fatty acid (Surfhope J-1216, HLB value = 16, Mitsubishi Kagaku Foods Corporation)	100 mg efficacy : 5 mg
Reference Example 2	Polysorvate 80 (Nikkol TO-10M, Nikko Chemicals Co., Ltd.)	100 mg efficacy : 5 mg
Reference Example 3	Polyoxyl 40 (Nikkol MYS-40, Nikko Chemicals Co., Ltd.)	100 mg efficacy : 5 mg
Reference Example 4	POE (105) POP (5) glycol (PEP-101, Freund Industrial Co., Ltd.)	100 mg efficacy : 5 mg
Reference Example 5	Sodium lauryl sulfate (Emal OS, Kao Corporation)	100 mg efficacy : 5 mg

Test Example 1

Suspensions were prepared such that the concentration of amorphous

cefditoren pivoxil in the suspensions was 10 mg/ml and individual additives were added to the suspensions at the formulation ratios shown in Table 1. More specifically, 350 ml of water or 350 ml of an aqueous solution of individual surfactant was added to amorphous cefditoren pivoxil on the basis of an amount equivalent to 3.5 g efficacy thereof to obtain each of the suspensions. The amorphousness-maintaining period was evaluated for the suspensions thus prepared.

[0031]

The amorphousness-maintaining period was measured as follows. Specifically, the suspensions were stored at 25°C under (air-tight) conditions and sampled immediately, 1 day, 2 days, 3 days, 5 days, 7 days, 10 days, and 14 days after the preparation. The sampled suspensions were centrifuged and the resultant residues were dried under reduced pressure and subjected to the powder X-ray diffraction analysis. The results are shown in Table 2.

[0032]

[Table 2]

	Immediately after the preparation	1D	2D	3D	5D	7D	10D	14D
Reference Example 1	A	A	C	C	C	C	C	C
Example 1	A	A	A	A	C	C	C	C
Example 2	A	A	A	C	C	C	C	C
Example 3	A	A	A	C	C	C	C	C
Example 4	A	A	A	C	C	C	C	C
Example 5	A	A	A	C	C	C	C	C
Reference Example 2	C	C	C	C	C	C	C	C
Reference Example 3	C	C	C	C	C	C	C	C
Reference Example 4	A	C	C	C	C	C	C	C
Reference Example 5	A	A	C	C	C	C	C	C

C: Crystalline A: Amorphous

Crystallization of amorphous cefditoren pivoxil was stimulated with the surfactants other than sucrose ester of fatty acids, while the amorphousness-maintaining period was extended with sucrose ester of fatty acids.

[0033]

Examples 6 to 13

Homogenous powder mixtures were obtained by mixing amorphous cefditoren pivoxil, surfactants, and polymers at the formulation ratios shown in Table 3.

[0034]

[Table 3]

	Surfactant	Polymer	Formulation ratio (drug:surfactant: polymer)
Example 6	Sucrose ester of fatty acid	-	100 mg efficacy: 0.1 mg: -
Example 7	Sucrose ester of fatty acid	HPMC	100 mg efficacy: 0.1 mg: 1 mg
Example 8	Sucrose ester of fatty acid	HPMC	100 mg efficacy: 0.1 mg: 100 mg
Example 9	Sucrose ester of fatty acid	HPMC	100 mg efficacy: 5 mg: 1 mg
Example 10	Sucrose ester of fatty acid	HPMC	100 mg efficacy: 5 mg: 50 mg
Example 11	Sucrose ester of fatty acid	MC	100 mg efficacy: 5 mg: 50 mg
Example 12	Sucrose ester of fatty acid	HEC	100 mg efficacy: 5 mg: 50 mg
Example 13	Sucrose ester of fatty acid	-	100 mg efficacy: 100 mg: -

Sucrose ester of fatty acid: DK Ester SS, HLB value = 20, Daiichi Kogyo Seiyaku Co., Ltd.
HPMC (hydroxypropylmethyl cellulose): TC-5R, Shin-Etsu Chemical Co., Ltd.
MC (methylcellulose): Metholose SH-4, Shin-Etsu Chemical Co., Ltd.
HEC (hydroxyethyl cellulose): HEC Daicel SP400, Daicel Chemical Industries, Ltd.

Test Example 2

Suspensions were prepared such that the concentration of the amorphous cefditoren pivoxil in the suspensions was 10 mg/ml and individual additives were added to the suspensions at the formulation ratios shown in Table 3. More specifically, a sucrose ester of fatty acid (DK Ester SS) and individual polymer were dissolved into 350 ml of water and the resultant aqueous solution was added to amorphous cefditoren pivoxil on the basis of an amount equivalent to 3.5 g efficacy thereof to obtain each of the suspensions. The amorphousness-maintaining period was evaluated for the suspensions thus prepared.

[0035]

The amorphousness-maintaining period was measured as follows. Specifically, the suspensions were stored at 25°C under (air-tight) conditions and sampled immediately, 1 day, 2 days, 3 days, 5 days, 7 days, 10 days, and 14 days after the preparation. The sampled suspensions were centrifuged and the resultant residues were dried under reduced pressure and subjected to the powder X-ray diffraction analysis. The results are shown in Table 4.

[0036]

[Table 4]

	Sucrose ester of fatty acid mixed*	Polymer mixed*	Immediately after the preparation	1D	2D	3D	5D	7D	10D	14D
Reference Example 1	-	-	A	A	C	C	C	C	C	C
Example 6	0.1 mg	-	A	A	A	C	C	C	C	C
Example 7	0.1 mg	HPMC 1 mg	A	A	A	C	C	C	C	C
Example 8	0.1 mg	HPMC 100 mg	A	A	A	A	C	C	C	C
Example 1	5 mg	-	A	A	A	A	C	C	C	C
Example 9	5 mg	HPMC 1 mg	A	A	A	A	C	C	C	C
Example 10	5 mg	HPMC 50 mg	A	A	A	A	A	A	A	C
Example 11	5 mg	MC 50 mg	A	A	A	A	A	A	C	C
Example 12	5 mg	HEC 50 mg	A	A	A	A	A	A	C	C
Example 13	100 mg	-	A	A	A	A	A	C	C	C

C: Crystalline, A: Amorphous

*: Formulated on the basis of an amount equivalent to 100 mg efficacy of amorphous cefditoren pivoxil.

The extension of the amorphousness-maintaining period was observed with the addition of only 0.1 mg of sucrose ester of fatty acids. Further, the further extension of the amorphousness-maintaining period was observed with the addition of various polymers.

[0037]

Reference Examples 6 and 7 and Example 14

A homogenous powder mixture was obtained by mixing individual components with the formulation ratios shown in Table 5, and then an appropriate amount of purified water was added to the mixture followed by kneading. The kneaded admixture was wet-granulated by an ordinary method to obtain granules. Tablets having flat surfaces were obtained by subjecting 200 mg of these granules to compression molding.

[0038]

[Table 5]

	Reference Example 6	Reference Example 7	Example 14
Amorphous cefditoren pivoxil	Equivalent to 100 mg efficacy	Equivalent to 100 mg efficacy	Equivalent to 100 mg efficacy
Sodium caseinate	50mg	-	-
Sucrose ester of fatty acid	-	-	5mg
Hydroxypropylmethyl cellulose	-	40mg	40mg
Excipient, disintegrant, binding agent, and the like	Appropriately	Appropriately	Appropriately
Total	1000mg	1000mg	1000mg

Test Example 3

Wettability was evaluated for the tablets obtained in Reference Examples 6 and 7 and Example 14. To the tablets obtained, 10 μl of water was added dropwise and the time required for the water drops to be completely absorbed into the tablets was measured. The results are shown in Table 6.

[0039]

[Table 6]

	1	2	3	Average	S.D.
Reference Example 6	431	422	427	427	5
Reference Example 7	745	584	648	659	81
Example 14	289	155	233	226	67

(Unit: Second)

The tablets containing sodium caseinate (Reference Example 6) exhibited faster water infiltration rates than the tablets without sodium caseinate and a sucrose ester of fatty acid (Reference Example 7). Furthermore, the tablets containing a sucrose ester of fatty acid (Example 14) exhibited markedly faster water infiltration rates than the tablets containing sodium caseinate. The composition according to the present invention was revealed to have markedly improved wettability as compared to those produced using conventional wettability-improving methods.

[0040]

Test Example 4

The granules obtained in Reference Example 6 and Example 14 were evaluated for their oral absorbability in human. Specifically, a crossover test was carried out with 24 healthy adults. To these adults, 1,000 mg of granules were orally administered with 150 ml of water under fasting conditions, and the blood was sampled after given hours to measure the concentration in blood by HPLC. The results are shown in Tables 7 and 8 and Figure 1.

[0041]

[Table 7]

	Reference Example 6		Example 14	
Time (hours)	Average concentration in blood	S.D.	Average concentration in blood	S.D.
0.5	0.49	0.28	0.79	0.32
0.75	0.76	0.36	1.21	0.37
1	0.90	0.33	1.24	0.31
1.5	0.95	0.27	1.10	0.29
2	0.81	0.23	0.84	0.28
2.5	0.65	0.20	0.65	0.20
3	0.48	0.14	0.47	0.17
4	0.26	0.09	0.27	0.10
5	0.16	0.05	0.16	0.08
6	0.09	0.04	0.09	0.04
8	0.01	0.03	0.01	0.03

(Unit: μg/ml)

[Table 8]

	Max. conc. in blood (Cmax) (μg/ml)		Area under curve of conc. in blood (AUC) (μg • hr/ml)		Time to reach max. conc. in blood (Tmax) (hr)	
	Average	S.D.	Average	S.D.	Average	S.D.
Ref. Example 6	1.07	0.28	2.85	0.66	1.46	0.48
Example 14	1.30	0.33	3.30	0.90	0.96	0.28

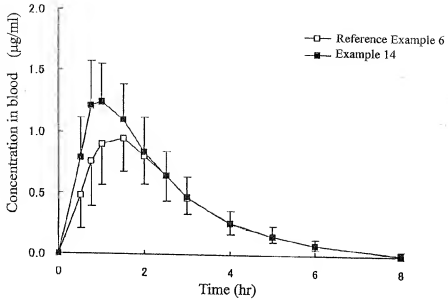
As compared to the conventional granules with improved oral absorbability (Reference Example 6), the composition according to the present invention (Example 14) exhibited the increases in the maximum concentration in blood (Cmax) and the area under the curve of the concentration in the blood (AUC) and the reduction in time

required to reach the maximum concentration in blood (Tmax), which shows that its oral absorbability is markedly improved.

[Brief Description of the Drawing]

[Fig. 1]

A view showing the change with time in blood cefditoren concentrations (n = 24, average ± S.D.) when the solid composition according to the present invention and the composition of Reference Example 6 were orally administered to healthy adults.


Concentration in blood (μg/ml)
2.0
1.5
1.0
0.5
0.0
0
2
4
6
8
Time (hr)
Reference Example 6
Example 14

[Fig. 1]

[Document Type] ABSTRACT 2002-290367

[Abstract]

[Object]

To provide a cefditoren pivoxil pharmaceutical preparation which can safely be administered to a patient and not only improves wettability of cefditoren pivoxil, but also further improves absorbability through the intestinal tracts by maintaining amorphous particles having high oral absorbability in a liquid for a long period of time.

[Means for Solving the Problems]

A solid composition comprising a physical mixture of amorphous cefditoren pivoxil and a sucrose ester of fatty acid.

[Selected Drawing]

None